Title – Temporal trends in initial and recurrent lower extremity amputations in people with and without diabetes in Western Australia from 2000 to 2010

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Abstract

Aims: To examine temporal trends in lower extremity amputations in people with type 1 diabetes, type 2 diabetes and cardiovascular disease (CVD) without diabetes in Western Australia (WA) from 2000-2010.

Methods: We used linked health data to identify all non-traumatic lower extremity amputations in adults aged ≥20years with diabetes and/or CVD from 2000 to 2010 in WA. Annual age- and sex-standardised rates of total, initial and recurrent amputations, stratified by major and minor status, were calculated for type 1 and type 2 diabetes, and CVD without diabetes, from the at-risk population for each group. Age- and sex-adjusted trends were estimated from Poisson regression models.

Results: 5891 lower extremity amputations were identified. Peripheral vascular disease (71%), hypertension (70%) and chronic kidney disease (60%) were highly prevalent. Average annual rates of total amputations were 724, 564 and 66 per 100,000 person-years in type 1, type 2 diabetes and CVD without diabetes respectively. Rates of initial amputations fell significantly by 2.4%/year (95% CI -3.5, -1.4) in type 2 diabetes, with similar declines for type 1 diabetes and CVD without diabetes (interaction p=0.96), driven by large falls in major amputations. There was limited improvement in recurrence rates overall, with recurrent minor amputations increasing significantly in type 2 diabetes (+3.5%/year, 95% CI +1.3%, +5.7%).

Conclusion: Lower extremity amputation rates have declined at a population level in people with diabetes and CVD without diabetes, suggesting improvements in prevention and management for this high-risk patient group, however limited declines in recurrent amputations requires further investigation. *Word count = 249*

Keywords: Amputation; Diabetes; Trends; Cardiovascular Disease; Epidemiology

1. Introduction

Complications of diabetes such as peripheral neuropathy and peripheral vascular disease and their sequelae of foot ulceration, sepsis and lower extremity amputation, are compounded by an ageing population and increasing prevalence of diabetes [1]. In Australia, diabetes-related lower extremity amputations pose a substantial personal and public health cost and contribute disproportionately to diabetes-related inpatient costs [2, 3].

Although rates of foot ulceration and subsequent wound healing are the best indicators of disease severity and quality of foot care, rates of amputations are easier to measure [4, 5]. Population level trends in initial and recurrent procedures, stratified by diabetes type and by major and minor amputation status, are scarce and have not been reported in Australia. Studies internationally show considerable variation in the incidence of amputations, attributed to methodological factors, healthcare systems, and choices of treatment [5]. Despite these variations, most reports indicate that the incidence of major amputations has fallen over the last two decades [6-9].

Assessing trends in amputations in people with and without diabetes is complex and results need to be interpreted carefully. The average incidence and its trend over time may be influenced by type and definition of diabetes, the level of amputation and whether an amputation is an initial (true incident) or recurrent (subsequent) one. It is also crucial that the denominator used for the calculation of amputation rates in people with diabetes is the population at risk, not the whole population [4, 5].

The aim of this study was to examine trends in lower extremity amputations in Western Australia (WA) using comprehensive state-wide linked data. Trends in initial and recurrent major and minor amputations were compared in patients with type 1 diabetes, type 2 diabetes and cardiovascular disease (CVD) without diabetes between 2000 and 2010.

2. Materials and Methods

Data for this study were obtained from the Western Australian Data Linkage System (WADLS), which systematically links administrative health data whilst conserving patient privacy [10]. All hospitalisations and death records for an individual are linked by computerised probabilistic matching with manual clerical checking, which has >99% accuracy. The linked dataset included all public and private hospital morbidity and mortality records for all patients admitted with diabetes, CVD or renal disease in WA between 1985 and 2010, and all non-cardiovascular disease records for these patients. Approval for this study was obtained from the Human Research Ethics Committees of The University of Western Australia and the WA Department of Health.

Patients in the linked dataset who underwent any lower extremity amputation in WA between 2000 and 2010 were identified using the Australian Classification of Health Interventions. Patients aged <20 years at the time of amputation were excluded from the study (n=38), as were lower extremity amputations for trauma and cancer. A minor amputation was defined as any amputation distal to the ankle joint (44338-00, 44358-00, 44364-00, 44364-01, 90557-00) and a major amputation as through or proximal to the ankle joint (44361-00, 44361-01, 44367-00, 44367-01, 44367-02). Multiple minor amputations performed during the same admission were counted as a single minor amputation, and a major and minor amputation recorded on the same admission designated as a major amputation only.

Amputations were identified as initial if the patient had a 15-year amputation-free history, and all other amputations classified as recurrent. Because the International Classification of Procedures in Medicine and International Classification of Diseases (ICD) version 9 was used in WA prior to July 1999, additional ICD codes were used to determine minor or major amputation status during the look-back period (minor: 5-845, 5-846, 84.11, 84.12; major: 5-847, 5-848, 84.13 - 84.17).

Diabetes was identified for each patient from any diagnosis field using 15 years of hospitalisation history prior to amputation (type 1, ICD-9 250.x1, 250.x3/ICD-10 E10; type 2 250.x2, 250.x4/E11). For individuals with inconsistent coding for diabetes type at different hospitalisations, type was assigned based on the most frequent code. Patients were classified as having CVD without diabetes if they had prior hospitalisations for CVD (ICD-9 398-459; ICD-10 I00-I99) but no diabetes coded during the 15-year period prior to their amputation. Identification of comorbidities was based on hospitalisation history and included coronary heart disease (ICD-10 I20-I25); peripheral vascular disease (I70-I79); chronic kidney disease (CKD, based on the Australian Institute of Health and Welfare definition) [11]; hypertension (I10-I15); cerebrovascular disease (I60-I69, G45); heart failure (I50); and atrial fibrillation (I48).

2.1 Statistical Analysis

Descriptive statistical analysis was performed separately for the three groups (type 1 diabetes, type 2 diabetes and CVD without diabetes) and presented as mean (±SD) for continuous variables and as frequencies (%) for categorical variables.

Annual amputation rates were calculated separately for each patient group and stratified by amputation type, using the number of amputations in each category for each calendar year as the numerator, and the person-years in the estimated at-risk population in each calendar year as the denominator. The at-risk populations for each group were estimated from the linked dataset by calculating diabetes and CVD prevalence. Annual counts of prevalent cases of type 1 diabetes were identified using a 15-year look-back period from 30th June in each study year to identify people with type 1 diabetes alive at this date. Similarly, a 15-year lookback period from 30th June in each study year was used to identify prevalent cases of type 2 diabetes. For CVD prevalence, people with prior hospitalisation for CVD but with no diabetes history were identified using the same method. This method has been used previously in linked health data to estimate diabetes prevalence for the calculation of myocardial infarction incidence rates in people with diabetes [12] and for atherothrombotic CVD prevalence [13]. The annual prevalence counts were further adjusted according to prior amputation history for each group. For example, the denominator for initial amputations in type 1 diabetes was the estimated prevalent type 1 diabetes population with no prior history of amputation. Annual amputation rates were age- and sex-standardised by the direct method using 5-year age groups, with internal weights derived from the person-years of the three groups as the standard population. Age- and sex-adjusted trends were estimated using Poisson log-linear regression models and interactions for age and sex checked and included if significant. Trend estimates were calculated from the exponential of the beta-coefficient for calendar year and are reported as annual percentage changes. Significance was set at $p<0.05$. Statistical analyses were performed using SAS statistical software V9.4 (Cary, NC, USA).

3. Results

There were 2095 major and 3796 minor lower extremity amputations performed in 4221 patients with diabetes or CVD without diabetes in WA from 2000-2010 (Table 1). The majority (57.7%) of amputations occurred in patients with type 2 diabetes. There was a considerable male preponderance in all groups, particularly in type 1 and type 2 diabetes. Patients with type 1 diabetes were younger at the time of initial (56.7 years) and recurrent (56.9 years) amputation than patients with CVD and no diabetes (70.7 and 71.9 years respectively) and type 2 diabetes (67.9 and 66.9 years respectively). Minor amputations were more common in patients with diabetes, however this difference was less evident for CVD patients without diabetes (minor : major ratio 1.4 for initial and 1.1 for recurrent amputations). There were high levels of peripheral vascular disease (71%), hypertension (70%) and chronic kidney disease (60%) across the patient cohort however levels of comorbidity were generally lower in CVD patients without diabetes. In all three groups there was a higher level of comorbidity at the time of recurrent versus initial amputation. There was an over-representation of Aboriginal and Torres Strait Islander people with type 2 diabetes undergoing amputation (12.8%).

Crude numbers of total amputations fell by 15% in type 1 diabetes (from 41 in 2000 to 35 in 2010), increased by 41% in type 2 diabetes (from 218 in 2000 to 372 in 2010) and fell by 17% in CVD without diabetes (294 in 2000 to 245 in 2010) (Supplementary Table 1).

3.1 Total amputations

Amputation rates in people with type 1 diabetes decreased from 1028 to 795 per 100,000, although the trend was not statistically significant (-3.2%/year, 95% CI -6.3, 0.0) (Table 2, Figure 1A). Significant downward trends were observed for the type 2 diabetes and CVD without diabetes groups. No difference in trends was detected between the three groups (p =0.16). Trends in total amputations were driven by large reductions in the rates of major amputations (Figure 1B): -5.2%/year in type 1 diabetes, -6.2%/year in type 2 diabetes, and -6.9%/year in CVD without diabetes. Rates of minor amputations were generally higher than major amputations in all groups, with small non-significant declines in the rates of minor amputations in each of the three groups (Figure 1B). Annual age-and sex-standardised rates are summarised in Supplementary Table 2.

3.2 Initial amputations

The rate of all initial amputations decreased at approximately 3%/year for each group, underpinned by large declines in initial major amputations (Table 2, Figure 2A). Although numbers were small in type 1 diabetes and the trend not significant (-8.2%/year, 95% CI -16.6, +1.1), rates fell from 266.7 to 43.6 per 100,000. There was a consistent decline in initial major amputations in type 2 diabetes (111.1 to 60.5 per 100 000), corresponding with an annual decrease of -6.6% (95% CI -8.9, -4.2). There were small downward trends in initial minor amputations but these were not significant in any group.

3.3 Recurrent amputations

The rate of all recurrent amputations remained unchanged in type 1 diabetes. The rate of all recurrent amputations was very high in people with type 2 diabetes (average annual age- and sex-standardised rate 35,440 per 100,000), and there was a non-significant upward trend in this group (+1.4%/year, 95% CI -0.4, +3.1) compared with CVD without diabetes (-2.7%/year, 95% CI -5.6, +0.2, p =0.02) (Table 2, Figure 2B). There was a significant +3.5% (95% CI +1.3%, +5.7%) increase in recurrent minor amputations in people with type 2 diabetes.

4. Discussion

Lower extremity amputation rates have declined in WA by ~3% annually between 2000 and 2010. Our analysis showed a similar rate of decline in amputations between type 1 and type 2 diabetes, and also in CVD patients without diabetes. The trends across the three groups were primarily driven by reductions in initial amputations, particularly in major procedures. Rates of total minor amputations did not decrease significantly in any of the three groups, and notably, recurrent minor amputation rates were high with a significant increase in people with type 2 diabetes.

Our study shows encouraging downward trends in rates of total amputations in type 1 and type 2 diabetes at a population level. Although most studies combine these two groups, the few examples where they are reported separately show contrasting results [14-16]. We observed a similar decline in amputations for type 1 and type 2 diabetes although the changes in type 1 diabetes were not significant – presumably due to the smaller numbers. These trends are an important finding at a population level as they imply effective prevention and management approaches across both patient groups.

In Australia, as elsewhere, the prevalence of diabetes has increased and is now estimated at 6.5% in WA [17]. Our analysis used type 1 and type 2 prevalent diabetes populations as the denominator for calculating rates, allowing the trends to reflect rates of amputations in people with diabetes. A large U.S. study showed that rates of amputations in people with diabetes fell by 50% between 1990 and 2010 when people with diagnosed diabetes were used as the denominator, yet there was no decrease in rates when the U.S. adult population was used as the denominator [18]. This pattern is similar to that demonstrated by Ikonen et al [14], highlighting the importance of accounting for changes in the underlying prevalence of diabetes in the population.

Our study is the first to clearly distinguish between trends in initial and recurrent amputations at a population level. This has important implications for patients with and without diabetes, as rates of initial amputations may reflect the effectiveness of primary prevention whereas recurrent amputations reflect treatment and secondary prevention approaches [9]. We have shown that whilst rates of initial, or first-ever, amputations are falling, trends in recurrent amputations appear less favourable. There are likely to be many factors contributing to these differences. A move towards coordinated multidisciplinary care of diabetic foot disease with improved protocols, referral pathways and patient education has evolved in Australia over the last two decades, and this may be a contributing factor in the falling initial amputation rates, particularly in type 2 diabetes. This approach has been shown to reduce amputation rates in other settings, even where absolute numbers of patients presenting with foot ulcers increased [18]. The rate of diagnosis of diabetes itself is increasing due to greater awareness and screening which may result in an increasing proportion of the diabetic population having lesser degrees or durations of hyperglycaemia. Given that the risk of amputation is very low in the first 10 years after diagnosis [19], this change in the distribution of disease severity could reduce the risk of foot ulceration and initial amputation [7], however the impact on patients requiring further amputation is as yet unknown.

Our observation that a decreasing incidence of major lower extremity amputations is driving the overall fall in total amputations is consistent with most epidemiological studies from Europe and the US [6,8,9,14,21] although some studies found no change in major amputation rates [22,23]. A study using unlinked national data in Australia reported a decreasing rate of above ankle amputations with concurrent increasing partial foot amputations in the whole population (equivalent to our major and minor classifications respectively)[24]. This pattern is also evident in our person-based linked data analysis of the WA population. However, the former study showed no reduction in total amputations. This contrast with our results is potentially due to inclusion of all recorded procedures, compared with the person-based approach of our study.

The differences between a minor and major amputation for the individual patient and healthcare system are enormous. It is therefore useful to distinguish between the two when assessing rates and trends in amputations. Whilst ulcer prevention or healing remain the main goal of foot care in diabetes, minor amputation has an important role in preventing progression of foot disease in order to avoid the need for a major amputation [25]. This may be most important in patients needing multiple amputations. It is of interest that the only category to show a significant increase in rates was minor recurrent amputations in type 2 diabetes. This increase may reflect changes in surgical practice relying on multiple minor amputations to avoid or at least delay the need for a major amputation [8]. However, it may also reflect the underlying disease burden. The presence of peripheral vascular disease or peripheral neuropathy in these patients is associated with the onset of diabetic foot ulcers. Poor glycaemic control and the presence of infection are highly predictive of non-healing in this group [26,27]. Given the high prevalence (>90%) of peripheral vascular disease in the patients with diabetes undergoing recurrent amputations in our study, better management of this and other risk factors associated with diabetic foot ulcers may help to attenuate increasing rates of minor amputations. Other secondary prevention strategies including off-loading and patient education are also priorities in patients with a history of a foot ulcer. Our results highlight the need for better understanding of the factors impacting on trends in minor amputations at a population level. .

Despite the improvements in overall trends, the average rates of amputations in people with diabetes were still up to 10 times higher than the group with CVD and no diabetes in our study. This is despite the fact that our comparator group (CVD and no diabetes) is relatively high-risk, predominated by the presence of peripheral vascular disease, chronic kidney disease and hypertension. Other studies which have used a broader no diabetes comparison group have found lower amputation rates than seen in our CVD group [14,16], although have generally reported larger reductions in amputations in people with diabetes than in the non-diabetes group, in contrast to our results. We have previously reported very high recurrence rates for hospitalised peripheral vascular disease in WA [28], and this finding may be due to the high rate of recurrent amputations as revealed in the current study.

The strength of this study lies in the quality of data linkage and the ability to use 15 years of hospitalisation records to distinguish between initial and recurrent amputations, major and minor amputations and type 1 and type 2 diabetes in a whole-population setting. This also allowed us to demonstrate trends based on an at-risk population for each amputation type and diabetes status group. Few previous studies have reported trends in this detail. Because of limited whole-population diabetes prevalence data, hospital data was used in this study to estimate diabetes prevalence. Hospital-identified diabetes underestimates the true prevalence of diabetes in the population and therefore the rates shown in this study may overestimate actual rates. However trends in amputations in people with diabetes would only be biased if there was a difference in prevalence trends between hospital-based versus whole-population diabetes prevalence. We therefore compared annual hospital-based diabetes prevalence with that from WA self-reported survey data [17], and found a similar increasing trend of ~2%/year in both data sources for type 1 and type 2 diabetes. This implies that the trends seen in the current study would not be biased by the use of hospitalised diabetes to estimate rates denominators. An important limitation, typical of most administrative datasets, is that side of procedure is not recorded, making it impossible to know whether recurrent amputations were ipsi- or contra-lateral. Whilst the WADLS is regularly audited for data quality [10], administrative data may be subject to coding misclassification. However, sensitivity and specificity for the recording of diabetes in hospital morbidity data in WA is high (90% and 95% respectively) in cardiac patients with the use of an extended look-back period [29], so it is likely that a high level of accuracy was also apparent in our study. However, we were unable to reliably measure the prevalence of diabetic peripheral neuropathy in our study. Although there is an ICD code for type 2 diabetes with polyneuropathy (E11.42), documentation in medical records and subsequent coding in administrative data is inconsistent.

There has been a reassuring decline in population rates of amputations in the high-risk groups of people with type 1 and type 2 diabetes and cardiovascular disease. However, the absolute number of amputations has increased by nearly 50% in patients with type 2 diabetes. This is likely to be due to a combination of increasing prevalence and life expectancy [30], which has important implications for the planning and funding of services for diabetic foot disease. The high level of vascular comorbidity across patients with diabetes and CVD highlights the need for targeted preventive strategies. Further investigation is needed to identify the factors associated with the increasing rate of recurrent minor amputations in patients with type 2 diabetes and to establish and report appropriate outcomes in this patient group.

Author contributions

DS conceived the idea for the study. LN carried out the data and statistical analysis, and wrote, reviewed and edited the manuscript. JK and DS wrote, reviewed and edited the manuscript. MK provided statistical advice, and reviewed/edited the manuscript. PN provided clinical advice, and wrote and edited the manuscript. TB advised on data analysis, and reviewed/edited the manuscript, and is the guarantor for the contents of the article. All authors had full access to the data, and assisted with interpretation of data and reviewed and gave their final approval of the version to be submitted.

Conflict of Interest

The authors declare that they have no conflict of interest associated with this article.

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Table 1.Characteristics of patients (n=4221) at the time of each admission for amputation (n=5891) between 2000 and 2010 in Western Australia.

	Type 1 diabetes (n=364)	Type 2 diabetes (n=3399)	CVD without diabetes (n=2128)
Initial amputations	n=179	n=1977	n=1693
Sex (male)	122 (68.2)	1335 (67.5)	982 (58.0)
Mean age (years)	56.7 (15.5)	67.9 (13.2)	70.7 (16.3)
Minor : major ratio	3.1	2.2	1.4
Aboriginal/Torres Strait Islander	10 (5.6)	244 (12.3)	35 (2.1)
Comorbidities			
Coronary heart disease	69 (38.5)	839 (42.4)	523 (30.9)
Peripheral vascular disease	114 (63.7)	1398 (70.7)	935 (55.2)
Chronic kidney disease	115 (64.2)	1141 (57.7)	824 (48.7)
Hypertension	127 (70.9)	1525 (77.1)	829 (49.0)
Cerebrovascular disease	25 (14.0)	393 (19.9)	291 (17.2)
Heart failure	40 (22.3)	613 (31.0)	367 (21.7)
Atrial fibrillation	19 (10.6)	484 (24.5)	405 (23.9)
Recurrent amputations	n=185	n=1422	n=435
Sex (male)	135 (73.0)	1032 (72.6)	271 (62.3)
Mean age (years)	56.9 (12.3)	66.9 (12.4)	71.9 (14.8)
Minor : major ratio	1.8	2.0	1.1
Number of patients	98	875	344
Aboriginal/Torres Strait Islander	9 (4.9)	194 (13.6)	6 (1.4)
Comorbidities			
Coronary heart disease	98 (53.0)	701 (49.3)	171 (39.3)
Peripheral vascular disease	170 (91.9)	1288 (90.6)	319 (73.3)
Chronic kidney disease	151 (81.6)	959 (67.4)	225 (51.7)
Hypertension	149 (80.5)	1218 (85.6)	253 (58.2)
Cerebrovascular disease	41 (22.2)	325 (22.9)	96 (22.1)
Heart failure	66 (35.7)	507 (35.6)	120 (27.6)
Atrial fibrillation	14 (7.6)	388 (27.3)	106 (24.4)

Data are n (%) for categorical variables and mean (±standard deviation) for continuous variables.

Table 2. Average annual age- and sex-standardised amputation rates and age-and sex-adjusted trends for each amputation type according to prior amputation history and diabetes status.

	Type 1 diabetes			Type 2 diabetes			CVD without diabetes			
	n	Average annual rate/100,000	Annual % change (95% CI)	n	Average annual rate/100,000	Annual % change (95% CI)	n	Average annual rate/100,000	Annual % change (95% CI)	Interaction *P*-value*
Total amputations	364	724.1	-3.2% (-6.3, 0.0)	3399	564.1	-2.4% (-3.5, -1.4)	2128	66.3	-3.8% (-5.1, -2.5)	0.16
Total Major	109	243.1	-5.2% (-10.7, +0.7)	1082	176.0	-6.2% (-8.0, -4.4)	904	28.4	-6.9% (-8.8, -5.0)	0.69
Total minor	255	479.2	-2.5% (-6.2, +1.4)	2317	390.9	-0.6% (-1.9, +0.8)	1224	37.9	-1.4% (-3.1, +0.4)	0.55
All initial amputations	179	370.4	-3.3% (-7.7, +1.4)	1977	335.6	-3.0% (-4.4, -1.6)	1693	52.8	-3.1% (-4.5, -1.6)	0.96
Initial Major	44	113.1	-8.2% (-16.6, +1.1)	610	99.8	-6.6% (-8.9, -4.2)	698	21.9	-6.0% (-8.1, -3.7)	0.84
Initial Minor	135	257.2	-1.7% (-6.8, +3.8)	1367	237.6	-1.4% (-3.0, +0.3)	995	30.9	-1.0% (-2.9, +1.0)	0.60
All recurrent amputations	185	9686.2	-0.2% (-4.6, +4.5)	1422	35,440.4	+1.4% (-0.4, +3.1)†	435	3947.9	-2.7 (-5.6, +0.2)†	0.06
Recurrent major	65	4498.8	+0.5% (-6.9, +8.6)	472	11,158.7	-2.8% (-5.6, +0.1)	206	1894.1	-6.6% (-10.6, -2.4)	0.11
Recurrent Minor	120	5907.1	-0.5% (-6.0, +5.3)	950	24,067.1	+3.5% (+1.3, +5.7)	229	1614.5	+0.7% (-3.3, +4.9)	0.33

*Interaction p-value for comparison of age- and sex-adjusted trends between type 1 diabetes, type 2 diabetes and CVD without diabetes. Model includes age, sex, calendar year, diabetes status and an interaction term for calendar year and diabetes status. All pairwise interactions were also tested and are shown if significant.

†Interaction p-value for comparison between type 2 diabetes and CVD without diabetes group p=0.02.

Figure Legends

Figure 1. Age and sex standardised rates for (A) total amputations, (B) total major amputations, and (C) total minor amputations, stratified by diabetes status, in Western Australia between 2000 and 2010. White circles = type 1 diabetes; black circles = type 2 diabetes; white squares = CVD without diabetes.

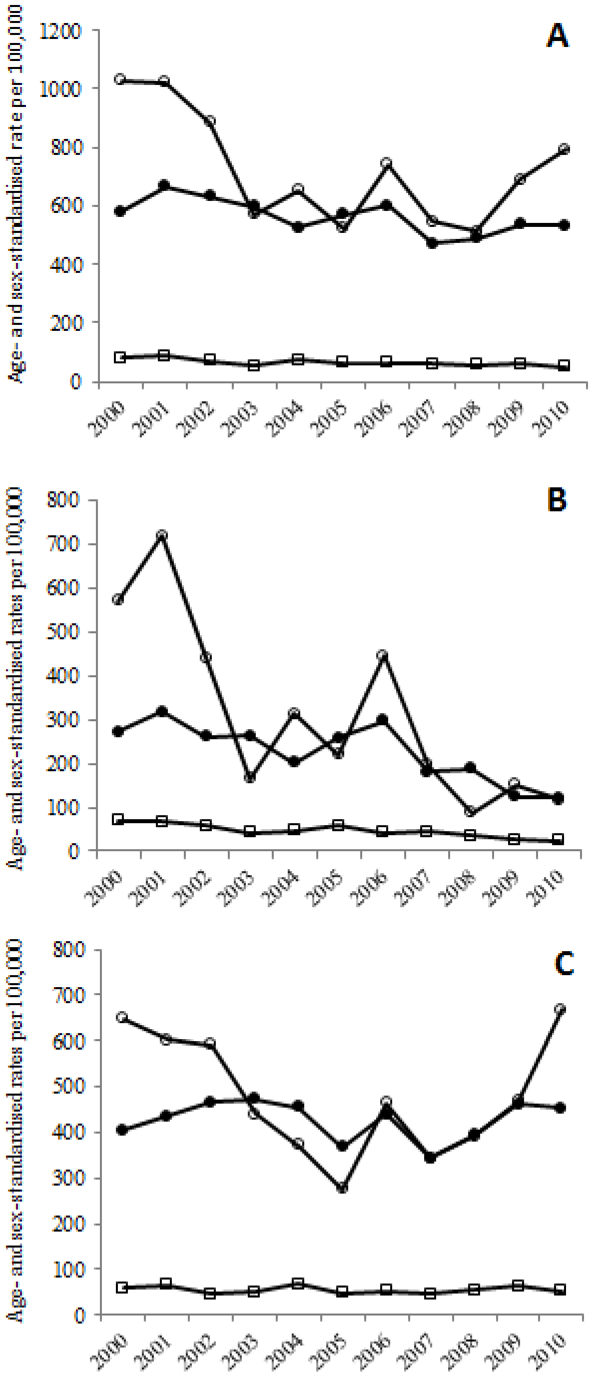

Figure 2. Age and sex standardised rates for (A) all initial amputations, and (B) all recurrent amputations, stratified by diabetes status in Western Australia between 2000 and 2010. White circles = type 1 diabetes; black circles = type 2 diabetes; white squares = CVD without diabetes.